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David J. Earp, Ph.D.
KLARQUIST SPARKMAN CAMPBELL
LEIGH & WHINSTON, LLP
Suite 1600, 121 SW Salmon St.
Portland, OR 97204-2988

EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,176	BOURSNELL ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/604,165.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/26/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Group I claims, claims 1-11, the species gH, and the species GM-CSF, in the response filed 12/04/2003 is acknowledged. The species restriction with respect to IL-2 has been withdrawn by the examiner, since the following stated prior art rejection is applicable to both IL-2 and GM-CSF. The group restriction between claim 12 and Group I claims also has been withdrawn by the examiner.

Before responding to applicant's traversal on the restriction requirement, the examiner acknowledges that the entire paragraphs, lines 1-14 of page 2, are incorporated into the restriction letter incorrectly. The paragraphs were inadvertently incorporated from the parent application to which this as-filed application claims priority under 35 USC 121. As such, and for the record, the paragraphs bear no substance to the restriction requirement, and will not be considered as parts of the restriction letter. The examiner also acknowledges that no search of the prior art has been conducted to the presently pending claims 1-19 at the time the restriction letter was written.

Applicant also questions about the validity of the indication of the PTO-326 as part of Paper No. 10. The reference is to merely reflect that the mailed restriction letter was labeled as Paper No:10 in the order of all of the incoming and outgoing papers as set forth in the file. In order to avoid the confusion, future outgoing papers will be identified in term of month/date, for example.

The modified restriction between Group I claims (which includes claim 12 now) and other claims, disregarding the non-substantive paragraphs as mentioned above, remains proper and correct. Applicant mainly traverses that there is no serious burden

to examine all claims, since all prior art search and initial examination have been conducted to the presently pending claims. The traversal is not found persuasive because of the reasons set forth above, and the reasons of record. No examination and prior art have been conducted for all of the presently pending claims at the time of filing. As such, the reasons as set forth on page 3 of the restriction letter are correct.

Claims 12-19 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Acknowledgment is made of applicant' s claim for foreign priority based on applications filed in Great Britain on 21 Feb. 1995, 28 July 1995, and 16 February 1996. The priority applications have been submitted and entered in the parent '165 application

The application does not contain a Brief Description of Drawings. See MPEP § 608.01(a).

The priority information need to be updated in order to reflect that the parent '165 application has been issued as US 6287557 B1.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 3, the "said essential viral gene" lacks an antecedent basis.

In claims 7, the "corresponding" is indefinite because it is not apparent how the "corresponding" define the structural and functional relationship between "gene" and the recited glycoproteins, nor is it apparent as to what is exactly is a "mutant virus" that harbors a gene "corresponding" to a glycoprotein (gH, gD, gB, or gL), particularly when the claim is read as a whole.

In claim 1, and claims dependent there from, the term "immunomodulatory protein" is indefinite because it is not apparent as to what are exactly are encompassed by the term. While the specification at page 8 states that "the immunomodulatory proteins are not normally those proteins presently used as immunogens (antigens) in themselves", the phrase "not normally" is unclear to one of ordinary skill in the art as to what are exactly encompassed by the "not normally". The "not normally" is relative in its meaning, and thus, it is not clear as to under which normal or non-normal conditions the immunomodulatory proteins are defined as immunogens or not, respectively.

In claim 8, the recitation of "complement components" is indefinite because it is not apparent as to what exactly the metes and bounds of the "components", nor it is apparent as to what is exactly complemented by the unspecified "components".

In claim 8, the phrase "receptor therefore of human or non-human specificity" is indefinite because it is not apparent as to what the "therefore" and/or "non-human animal specificity" modify for. Should applicant intends to mean a receptor of a cytokine, chemokine, complement component, immune system accessory and adhesion molecule, it is suggested that another dependent claims should be added to reflect the intended

meaning. With respect to "specificity", it is not apparent as to which reference point the specificity is referred to.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-9, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims when given a broadest reasonable interpretation encompass a genus of unspecified RNA or DNA mutant viruses having a deletion of an unspecified essential gene, wherein the deletion renders the mutant DNA or RNA viruses replication defective without the presence of the essential gene. Claim 4 encompasses any herpes virus including hepatitis viruses A, B, and C. The claims can be reasonably construed as encompassing "genes" encoding a genus of unspecified "complement components" and of unspecified receptors for any and/or all cytokines, "complement components, adhesion molecules, chemokines of human and/or "non-human animal specificity".

Note that to the extent that the claims encompass "genes" encoding receptors of any and/or non-human animals specific to the cited immunomodulatory proteins, the claims readable on "genes" encoding the receptors are also applicable to this rejection.

While the specification and the knowledge in the prior art provide sufficient description of number of replication defective viruses including pox virus, AAV, retroviruses, adenovirus, and HSV, such known replication defective or mutant virus that could be used within the context of the teaching provided by the as-filed specification, *e.g.*, gene delivery vector, do represents the claimed genus as pending: the specification and the knowledge of the prior art do not provide sufficient description of the genus of RNA and/or DNA mutant viruses (which comprises an enormous number of RNA and/or DNA mutant viruses) having a deletion of any essential gene, wherein the deleted viruses only propagate in a cultured (complementing or packaging) cell expressing an essential gene. Other that HSV vector, which is mainly the focus of the teachings obtained from the as-filed specification, the as-filed specification provides no written description regarding complementing cells, sequence structures of mutant viruses and/or essential genes obtained there from, which cells and/or structures are clearly essential for the making and use of the claimed mutant viruses.

An adequate written description of the invention defined by the claims, *e.g.* genus of mutant RNA or DNA viruses which only propagate in a cell expressing an essential gene of the respective mutant viruses, requires more than a mere statement that it is part of the invention and reference to sequence information of several species of DNA or RNA viruses, and/or their homology of to that of the well-recognized HSV,

adenoviruses, and vaccinia viruses. What is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of DNA or RNA mutant viruses that only propagate in the presence of a recombinant essential gene. It is not sufficient to rely upon well-recognized replication defective adenoviruses, pox viruses,, as taught in the prior art of record, because disclosure of only the mutant HSV vectors, as in the instant case, is simply a wish to know the identity of an enormous number of mutant DNA or RNA viruses other than the well-known replication defective viruses cited in the prior art of record, in order to obtain a patent directed simply to a genus of mutant viruses, which could be reasonably construed as being dominant over prior art and/or patents that already teach some of the species of mutant viruses (mutant (replication defective) retroviruses, adnoviruses, AAV, and pox viruses. Notwithstanding the reasons set forth above, and even in 1996 or 1997, the state of the art exemplified by Mastrangelo *et al.* (1996, Seminars in Oncology), and Verma *et al.* (Nature, Vol. 389, pp. 249-242, 1997) teach that only adenoviral vectors, AAV vectors, retroviral vectors, lentiviral vectors, HSV vectors, vaccinia based vectors are available for use as replication defective vectors, wherein an understanding the basis biology of the structure and replication of viruses have been elucidated (entire document, especially page 242). It is not apparent to one skilled in the art that on the basis of the written description of this instant application and the knowledge of the prior art, all other mutant variants RNA or DNA viruses are readily available for practice the claimed invention. Even simple availability of some genomic sequences of other undeveloped replication defective mutant viruses is not the same as a detailed description of

essential materials such as essential genes, cloning sites, and/or suitable packaging cells that are necessary for the making of a replication defective mutant virus that must exhibit a property of not being able to propagate by itself but can be propagated into a sufficient number of useful replication defective particles in the presence of a recombinant essential gene of the mutant virus.

As to claims readable on a genus of heterologous genes obtained from human and/or non-human animals, which genes encode a genus of non-human animal and/or human chemokines; complement components; immune system accessory molecules; adhesion molecules; and receptors specific to chemokines, complement components, immune system accessory molecules, and adhesion molecules, the instant specification at best provides a sufficient description of a genus of human and/or murine cytokines, chemokines, adhesion molecules, human Ox-40, and human gp34 encoded cDNA, all of which cDNA were well-known in the art. However, neither the specification nor its incorporated references provide any sequence information of other cited immunoregulatory genes. In order to practice the claimed invention readable on a genus of DNA sequences listed in claim 8, one skilled in the art must turn to the specification and the knowledge in the prior art for the availability of a representative number of DNA species. However, it appears that the specification coupled with the knowledge in the prior art only provides sufficient description of cDNA encoding cytokines, chemokines, adhesion molecules, human Ox-40, and human gp34 encoded cDNA. Without the disclosure as to the availability of a genus of "non-human animal" genes encoding immune system accessory molecules, cytokines, complement components,

chemokines, adhesion molecules, and their respective receptors, applicant was not clearly in possession of the claimed genus of the cited non-human animal "genes" and/or human genes encoding unspecified "complement components" and the recited receptors.

In addition, an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property, i.e. encodes a genus of animal or human cytokines, complement components, immune system accessory molecules, chemokines, adhesion molecules, receptors of animal or human animal or human cytokines, complement components, immune system accessory molecules, chemokines, adhesion molecules, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Even with specific genes that encode cytokines or adhesion molecules, the prior art appears to indicate that only cDNA sequences coding for their respective proteins are sufficiently described as a genus. Claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed genus.

Claims 1, 3, 4, 6-9, 12, and 20 are also rejected under 35 U.S.C. 112, first paragraph, because the specification is only for claims drawn to the following subject matter:

- Replication defective DNA or RNA mutant virus known in the prior art at the time the invention was made and has written support from the as-filed specification, *e.g.,* adenoviruses, pox viruses, and HSV viruses, which DNA or RNA mutant virus further comprises a heterologous cDNA encoding an immunomodulatory protein, *e.g.,* cytokines, adhesion molecules, chemokines, human Ox-40, and human gp34 encoded cDNA , wherein the heterologous cDNA is inserted at the deletion site of an essential gene of the mutant virus.
- A process for preparing an immunogen comprising transfecting a tumor cell expressing a tumor antigen with the DNA or RNA mutant virus as set forth above.

The specification does not reasonably provide enablement for claims encompassing a genus of DNA or RNA mutant viruses as recited in claim 1 and claims dependent therefrom, nor does it reasonably provide enablement for a process of making a DNA vaccine that exhibits a “prophylactic effect” and/or a “therapeutic” effect

in any and/or all tumor therapies, wherein any and/or all genetically modified tumor cells including autologous and non-autologous genetically modified cells.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description for the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended without undue experimentation.

With regard to claim 12 drawn to a method of making a DNA vaccine for prophylactic and/or therapeutic tumor therapy comprising transfecting a tumor cell expressing a tumor antigen, neither the specification nor the prior art of record provides sufficient guidance an/or substantial evidences demonstrating that a representative number of cells comprising a tumor antigen and any and/or DNA or RNA tumor viruses exhibit a prophylactic effect in tumor therapy, nor is it apparent as to how one skilled in the art reasonably extrapolates from the disclosure of this instant specification to the "prophylactic" effect as contemplated by the claimed invention. The state of the art exemplified by Mastrangelo *et al.* (Seminars in Oncology, Vol. 23, No. 1, pp. 4-21, 1996) states that "to date the major successes with gene therapy for cancer have been limited to *in vitro* systems where tumor cells with well defined genetic defects are easily targeted" (page 13, column 2, first paragraph). In addition, Colombo *et al.* (Cancer Immunol Immunother, 41, 265-270, 1995) teach:

- "As for the cure of established tumors, the therapeutic efficacy of vaccination depends on the size, growth rate, invasiveness and location of the tumor" (page 265 bridging page 266);
- "It is clear that tumor inhibition and/or the induction of systemic immunity are not in themselves sufficient for evaluation of treatment efficacy and curative potential" (page 268, column 1, first paragraph;
- "Moreover, induction of systemic immunity with activation of CTL might not be sufficient to destroy existing tumor nodules, although tumor-bearing mice still retain the ability to recognize the same antigen present within the tumor when presented on a normal tissue and outside the tumor environment. This suggests that, while a tumor patient could be immunized against that tumor, the induced immunity is insufficient to fight an established tumor growing within its own stroma" (page 269, column 1, second paragraph);
- "An additional aspect to consider in vaccination protocols is the possible presence of more than one antigen on the same tumor cells, which may result in a skewed orientation of the immune response, i.e., a CTL response to different antigens depending on the site of immunization even with the same tumor cell type" ((page 269, column 1, last paragraph); and
- "Although some preliminary results indicating a mixed cellular response have been presented at different meetings, no correlation with immune-monitoring of antitumor T cell response is available to date" (page 268, column 2, last paragraph).

The as-filed specification does not provide sufficient guidance and/or evidence to address the above issues that must be overcome in order to successfully make a "vaccine " for use in prophylactic treatment of any subject at risk of having a tumor, and wherein the tumor has not been established. Thus, it is not apparent as to how one skilled in the art makes and/or uses, without any undue experimentation, a generic DNA vaccine for prophylactic use in tumor therapy as recited in the claims, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 8, and 9, and 12 are rejected under 35 USC 102(e) as being anticipated by Barber *et al.* (US 6,531,307 B1).

The main thrust of the invention is the concept of employing a known replication defective viral vector, *e.g.*, retrovirus vector, adenovirus vector, and AAV vectors, to

express an exogenous cytokine gene, wherein the gene is inserted within a deletion site of an essential gene of a virus which is used as the expression replication defective viral vector.

This concept is well recognized in the prior art, as evidenced by the teaching of Barber. Barber teaches, for example, an adenovirus vector, which is employed as a replication defective vector, to express an exogenous cytokine gene (GM-CSF, IL-2) for use in tumor treatment, wherein the GM-CSF gene is inserted within deletion site of the adenovirus E1 gene (see the claims on column 35 and 36, last par. of column 13 through column 14, first full par. of column 15, and second par. of column 16.

On column 16, lines 2-5, Barber teaches that the replication defective adenovirus is routinely constructed by following the teaching given above, for example, and the knowledge in the prior art.

As such, the claimed invention, drawn to known mutant virus vectors other than HSV vectors, is anticipated by Barber.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was

made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C.103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C.103(c) and potential 35 U.S.C.102(f) or (g) prior art under 35 U.S.C.103(a).

Claims 1-9, and 12 are rejected under 35 U.S.C. 103 as being unpatentable over Inglis *et al.* (WO 95/03399, published 2 February 1995), taken with Barber (US 6,531,307) and any of the following citations:

- applicant's admission of prior art in this instant specification at page 3, lines 20-35, page 4 bridging page 5, page 6, lines 11-18, page 10, lines 10-20, page 11, lines 10-27, page 31, lines 9-15, and lines 33-36;
- Haddada *et al.* (WO 93/19191, copy translated by the Ralph Mcelroy Translation Company);
- DeLuca (US Pat No. 5,658,724);
- EP 0 453 242 A1;
- Ho *et al.* (US Pat No. 5,661033);
- McLean *et al.* (The J. of Infectious Diseases, Vol. 170, pp. 1100-9, 1994;

- Godfrey *et al.,* J. Exp Med, 180, 2, pp. 757-762, 1994, and references cited therein including S Miura *et al.,* Mol Cell Bio 11, 3, pp. 1313-1325, 1991;
- Breggen *et al.,* Current Opinion In Immunology, 4, 5, 608-612, 1992;, 1994;
- Forester *et al,* J. Virology, 66, p. 341, 1992;
- WO 94/21807;
- Goebel *et al.,* Virology 179, 1990, pp. 249; and
- WO 94/16716 as to the availability of DNA sequences of pox viruses and coding sequences of their regulatory genes, and DNA sequences encoding cytokines and tumor antigens.

Inglis *et al.* disclose a process for constructing a herpes simplex virus vector which contains a deletion of the coding sequence of a protein essential for the production of virus particles. With respect to the mutant herpes simplex virus, the coding sequence that is deleted from the mutant simplex herpesvius (HSV) includes coding sequences of the HSV glycoproteins gH and gL, coding sequences of the HSV regulatory virus proteins IPCO (RL2), ICP4 (RS1), ICP27 (UL54), ICP34.5 (RL1), Vp16 (UL48), *e.g.,* page 7 bridging page 8.

The mutant viruses described in Inglis *et al.* are employed to express heterologous genes encoding immunomodulatory molecules including cytokines or molecules involved in lymphocyte signaling (see pages 10, and 22-29).

Page 11 of the as-filed specification discloses that techniques for inserting the heterologous gene at the site of deletion and for using complementing cell lines

containing the deleted essential gene are known in the art at the time the invention was made. Note that the genomic sequences of herpes simplex viruses, and molecular biology techniques of using restriction sites to make deletion and insertion of heterologous genes are well-known in the art at the time the invention was made (1995), see the cited references in this stated rejection. For example, see Haddada *et al.,* Ho *et al.,* DeLuca, and WO 94/16716. Furthermore, Inglis *et al.* teach:

"WO92/05263 describes the creation of a mutant virus in which the glycoprotein H gene is deleted from HSV in order to create a disabled virus for prophylactic and therapeutic vaccination against herpes simplex virus. This disabled virus can be propagated in complementing cells carrying and expressing a functional gH gene, and the virus produced from these cells used to successfully vaccinate both prophylactically and therapeutically, against herpes simplex virus-induced disease in mouse and guinea pig models. (WO 92/05263; Farrell *et al.,* J. Virol. 68, 927-932, 1994)".

The two essential limitations of the claimed invention of the presently pending claims are the limitation of an immunomodulatory protein (cytokine GM-CSF or IL-2) encoded DNA and an insertion of the immunomodulatory protein encoded DNA at the deletion site of an essential gene of any known virus, *e.g.,* HSV, vaccinia, and adenovirus. With regard to the limitation of the cytokine encoded DNA, Inglis *et al.* teach on page 10 that the infectious particles are used to introduce genes encoding immunoregulatory molecules such as cytokines. While Inglis *et al.* do not explicitly teach the availability of immunomodulatory protein encoded DNA at the time the invention was made, immunomodulatory protein encoded DNA are well-known in the art

at the time the invention was made, as exemplified by the prior art of record, and as admitted by the specification of this instant as-filed application at page 3, lines 20-35, page 6, lines 11-18, page 10, lines 10-20, page 11, lines 10-27, page 31, lines 9-15, and lines 33-36, and as evidenced by the prior art references cited in this stated rejection. For example, Haddada *et al.* or WO 94/16716 teaches that cytokine encoded DNA (IL-2) are routinely employed in the art as anti-tumor agents and as adjuvant so as to increase an immune response against a tumor or a pathogenic microorganism. In addition, applicant's admission over the prior art of record on page 3 from the as-filed specification are exemplified references that indicate it is well known in the art IL-2 or GM-CSF are effective adjuvant to stimulate T cell immunity *in vivo*.

Regarding the second limitation of placing an immunomodulatory protein encoded DNA at the deletion site of an essential gene of a known DNA or RNA virus, Inglis *et al.* do teach explicitly the placement of an immunomodulatory protein encoded DNA at the deletion site of an essential gene of a known DNA or RNA virus.

However, this concept is well recognized in the prior art, as evidenced by the teaching of Barber. Barber teaches, for example, an adenovirus vector, which is employed as a replication defective vector, to express an exogenous cytokine gene (GM-CSF) for use in tumor treatment, wherein the GM-CSF gene is inserted within deletion site of the adenovirus E1 gene (see the claims on column 35 and 36, last par. of column 13 through column 14, first full par. of column 15, and second par. of column 16.

Second par. of column 16 specifically teaches that this concept of employing a

replication defective adenovirus vector to express a cytokine gene can be utilized for the construction of other know viral vectors in the prior art, such as AAV vectors.

In addition, the totality of the prior art of record, *e.g.,* Inglis and the prior art of reference, clearly teach that an HSV vector deficient in an essential gene can be complemented by a cultured cell expressing the essential gene, and that routine recombinant techniques (see the prior art of record, including the Sambrook *et al.* Laboratory Manual as recited on page 22 of this instant specification can be used to perform deletions of an HSV essential gene (which is also well-known in the prior art of record as exemplified by Inglis *et al.* and DeLuca, for example) and/or insertions of any exogenous cDNA at any chosen site of the HSV vector as long as the insertion at the chosen site does not affect the propagation of the vector particles in a cultured cell expressing the deleted essential gene,

Therefore, at the time the invention was made, it would have been obvious matter of design choice to insert any known immunomodulatory protein encoded DNA at the deletion site of any essential gene of a known DNA or RNA virus, such as HSV vector, since applicant has not disclosed that insertion of a known immunomodulatory protein encoded DNA at the deletion site of any essential gene of a known DNA or RNA virus, such as HSV vector, solves any stated problem or is for any unexpected outcome, and since it is apparent that insertion of a known immunomodulatory protein encoded DNA at the deletion site of a non-essential gene or an essential gene of a known mutant virus vector would produce the same outcome, *e.g.,* expression of the

immunomodulatory protein. Note that it is immaterial whether insertions of a DNA encoding a cytokine occur at the deletion site of an essential gene or the deletion site of a non-essential gene, particularly in the absence of evidence to the contrary.

Further, It would also have been obvious for one of ordinary skill in the art to have inserted an expression cassette encoding a cytokine at the deletion site of the herpesvirus vector of Inglis *et al.* with a reasonable expectation of success, particularly in view of the disclosures of the WO 92/05263 and Barber reference, which provide support disclosure for such insertion. In addition, one of ordinary skill in the art would have been motivated to have employed the deletion site of the herpesvirus essential gene as an insertion site for an expression cassette encoding the cytokine in the method of Inglis *et al.* because WO 92/05263 which was cited as an illustrated example in Inglis *et al.* does teach and provide evidence showing that an insertion of a DNA expression cassette within the deletion site of the herpesvirus essential gene is a standard technique known in the art (pages 36 and 37, and Figure 7), and because the insertion would naturally ensure that efficient expression of the inserted gene would occur, see Barber, second par. of column 15, and that homologous recombination that results in a reinsertion of the deleted essential gene will not occur to impede the efficient expression of the inserted gene.

It would also have been obvious for one of ordinary skill in the art to have employed one or more immunogen encoded DNA including GM-CSF and/or IL-2 encoded DNA and/or antigen encoded DNA in the HSV vector of Inglis *et al.* One of ordinary skill in the art would have been motivated to have employed IL-2 or GM-CSF,

and antigen encoded DNA in the HSV vector of Inglis *et al.* because the prior art of record, as evidenced by Barber and applicant's disclosure on pages 3 and 31 of the specification, does teach that IL-2 or GM-CSF are effective cytokine to tumor treatment *in vivo,* and because an insertion of more than two tumor treatment protein encoded DNA would naturally provide an additive or combination effect of stimulating humoral immune responses in addition to the immunostimating effect of the cytokine encoded DNA.. Note that both Inglis *et al.* and WO 92/052,263 do indicate that HSV vectors can be employed to express a heterologous antigen for stimulating an immune response against the antigen.

Thus, the claimed invention as a whole was *prima facie* obvious.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson* may be reached at **571-272-0184**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER